DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 4/2/2010, is acknowledged and has been entered. Claims 24, 28, and 31 were amended. Claims 26-27 and 29-30 have been canceled. Accordingly, claims 24-25, 28, and 31 are currently pending and subject to examination below.

Objections/ Rejections Withdrawn

2. Objections to and rejections of claims 26-27 and 29-30 are moot in light of Applicant's cancellation of these claims.

Priority

3. The present application was filed on 9/28/05 as a National Stage (371) application of PCT/JP04/04606, filed 3/31/04. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Japanese Application No. 2003-094059, filed on 3/31/03.

Claim Objections

4. Claims 24-25 and 28 are objected to because of the following informalities:

5. Claim 24 recites an immunoassay method for measuring lipoprotein(a). The body of the claim sets forth a step (b) in which agglutination of particles is detected. Based on the specification, it is clear that this detection of particle agglutination is being used to indicate the presence of lipoprotein(a). However, this is not clearly explained in the claim, which does not make explicit how detection of agglutination correlates with measurement of lipoprotein(a). It is

suggest that the claim recite either an active method step in which lipoprotein(a) is actually measured or alternatively, a correlation step that describes how the results of the immunoassay method relate back to lipoprotein(a) measurement.

6. Claims 24-25 and 28 recite "the antigen-antibody reaction". It is presumed based on the specification that Applicant refers to the reaction between lipoprotein(a) in the biological sample and the anti-lipoprotein(a) antibody on the latex particles. However, this is not made clear because claim 24 does not refer to lipoprotein(a) as an "antigen". Clarification is requested.

7. Claim 25 refers to "a reaction solution". Applicant presumably intends to refer back to the same reaction solution which was earlier introduced in claim 24, line 7. It is suggested that the dependent claim refer to "the" reaction solution in order to make this clear.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 24-25, 28, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borque et al. ("Automated turbidimetry of serum lipoprotein(a)" Eur J Clin Chem Clin Biochem. 1993 Dec;31(12):869-74) in view of de Steenwinkel et al. (US 4,362,531), Metzner et al. (US 6,447,774), and Schmitdberger et al. (US 5,180,679).

Borque et al. teaches a turbidimetric immunoassay for quantifying lipoprotein(a) using latex particle agglutination (abstract and especially at page 869, "Summary"). The immunoassay involves contacting the sample with rabbit polyclonal IgG antiserum against human lipoprotein(a) coated onto latex particles (see pages 869-870, "Antibody", "Latex reagent", and "Assay Procedure"). The amount of lipoprotein(a) is then determined by observing the mixture for turbidity due to latex particle agglutination using an automatic analyzer, which measures absorbance at 700 nm (see page 870, "Assay procedure"; page 871, "Correlation"; Figure 1; and page 872, right column).

The teachings of Borque et al. differ from the claimed invention in that (1) the reference fails to specifically teach adding arginine to the assay system and (2) the reference is silent as to the particular concentration of the antibody used in the assay.

With respect to (1), de Steenwinkel et al. also relates to particle agglutination immunoassays and teaches that undesired interference effects in such assays due to non-specific protein-protein interactions can be reduced or overcome by including in the assay mixture a chaotropic or chaotropic-like agent (the abstract; column 1, lines 18-41; column 2, line 42 to column 4, line 50).

However, de Steenwinkel et al. do not specifically exemplify arginine as the chaotropic agent.

Metzner et al. teaches that known chaotropic agents include arginine (column 1, lines 55-56; column 2, lines 12-13).

Therefore, it would have been obvious to one of ordinary skill in the art to add a chaotropic agent to the agglutination immunoassay of Borque et al. because de Steenwinkel et al. taught that such agents reduce or overcome interferences in particle agglutination immunoassays. It would have been further obvious to employ arginine as the chaotropic agent in the method of Borque et al. and de Steenwinkel et al. because Metzner et al. taught that arginine is known to be a chaotropic agent. The selection of a known material for its known purpose would have been obvious.

With respect to (2), Borque et al. do not explicitly state what the final concentration of the antibody in the assay mixture was, but do indicate that the amount of antibody added was adjusted by providing antibody in a protein/ latex ratio of 1/10; 30 ml of a 0.5% particle solution was then added to the assay (page 870, "Latex Reagent" and "Assay procedure").

Schmidtberger et al. also relates to particle agglutination immunoassays and teaches that different amounts of antibody can be bound to the particles in order to influence the time at which agglutination occurs (column 2, lines 13-62).

Therefore, given that the amount of antibody used in a particle agglutination immunoassay was well recognized in the art to be a result-effective variable (as taught by both Borque et al. and Schmidtberger et al.), it would have been further obvious to one of ordinary skill in the art to employ polyclonal IgG antiserum against human lipoprotein(a) in amounts

falling within the claimed ranges of 0.15 or 0.16 mg/ml or greater out of the course of routine optimization.

With respect to the recitation in the preamble that the method is for measuring lipoprotein(a) "having several phenotypes", Borque et al. teach that lipoprotein(a) has several phenotypes, in that there are different genetic isoforms of apoliprotein(a) (see page 872, right column, second paragraph). This passage indicates that when performing the methods of Borque et al., such different apolipoprotein(a) isoforms would in fact all bind to the particles. Moreover, the methods of Borque et al. employ polyclonal antibodies, which are well known to bind to their cognate antigens in numerous different ways. As such, the evidence of record strongly suggests that the methods of Borque et al. would necessarily detect multiple isoforms or "phenotypes" of lipoprotein(a). See MPEP 2112.

Applicant is also reminded that statements in the preamble do not provide antecedent basis for terms in the body of the claim and are not essential to understand the limitations or terms in the claim body. The normal purpose of a claim preamble is to recite the purpose or intended use of the claimed invention. Such statements merely define the context in which the invention operates and usually will not limit the scope of the claim (MPEP 2111.02 and DeGeorge v. Bernier, Fed. Cir. 1985, 226 USPQ 758, 761 n.3). Notwithstanding the above, therefore, the preamble may be reasonably interpreted simply as a referring to the intended use of the recited detection method and does not clearly limit the scope of the claims.

Finally, Applicant is also reminded that claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. See MPEP 2111.04. In the instant case, the

preamble reference to measuring lipoprotein(a) "having several phenotypes" statement "whereby said variation is a function independent of lipoprotein(a) phenotype" does not clearly require that several phenotypes of lipoprotein(a) are actually measured during the performance of the method. Rather, this statement could be interpreted simply as an expression or characterization of the fundamental biochemical properties of lipoprotein(a), namely that this molecule can exist in several different isoforms or phenotypes.

Moreover, the instant claims set forth a latex immunoturbidimetric method of using a generic anti-lipoprotein(a) antibody in the claimed amount. It is therefore presumed absent evidence to the contrary that an assay method of this same format performed using the indicated reagents of step (a) and in their recited amounts would also necessarily measure lipoprotein(a) "having several phenotypes" as claimed.

With respect to claim 28, which specifies that the amount of arginine is less than or equal to 17% by weight, de Steenwinkel et al. further teach that the amount of chaotropic agent to be added to agglutination immunoassays should be checked for individual cases, since the optimum amount may vary (column 3, lines 29-38). Such teachings indicate that the amount of a chaotropic substance was recognized in the art to be a result-effective variable.

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05.

In addition, it is also noted that de Steenwinkel et al. provides guidance with regard to the selection of appropriate amounts of chaotropic agent to be used, teaching that in most cases, amounts of from about 0.5 up to about 2M are satisfactory (column 3, lines 34-36). It is asserted that the molecular weight of arginine was known in the art to be 174.2 g/mol. This is taken to be admitted prior art as Applicant has failed to traverse this assertion.

Since 1% of a solute is equal to 1 g per 100 ml, this would mean that in the case of arginine the range of 0.5-2M taught by de Steenwinkel et al. would correspond to 8.7%-34%[1], a range which overlaps that claimed instantly.

Therefore, absent evidence of criticality for the currently claimed amounts it would have been further obvious to one of ordinary skill in the art to arrive at the claimed amounts of arginine (i.e., less than or equal to 17% by weight) out of the course of routine optimization, and in particular by following the guidance of de Steenwinkel et al. regarding suggested amounts of chaotropic agent.

With respect to claim 31, Borque et al. teaches a polyclonal antibody (see page 869, "Antibody").

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[1] (0.5 moles/L) x 174.2 g/mol = 87.1 g/L and (2 moles/L) x 174.2 g/mol = 348.4 g/L
1 g/ 100 mL = 1%
87.1 g/L = 8.71 g/ 100 mL = 8.7% and 348.4 g/L = 34.8 g/ 100 mL = 34%

Response to Arguments

11. Applicant's arguments filed 4/2/2010 have been fully considered but they are not persuasive.

12. With respect to the objections to claims 24-25 and 28, Applicant does not specifically traverse the grounds on which the objections were made, but states that the amendments render moot the objections (Reply, page 3, section II). This is not found persuasive for reasons set forth above.

13. With respect to the rejections of claims 24-25, 28, and 31 under 35 U.S.C. 103(a) as being unpatentable over Borque et al. in view of de Steenwinkel et al., Metzner et al., and Schmitdberger et al., Applicant's arguments (Reply, pages 4-5) have been fully considered but are not persuasive of error.

Applicant argues that the claimed methods measure a plurality of lipoprotein(a) phenotypes that the primary reference explicitly discounts. See Reply, page 4, first paragraph.

Applicant's arguments were previously advanced in apparently verbatim form in the Reply filed 7/27/2009 (see page 5) and are not persuasive for reasons of record (Office action mailed 10/5/2009 at pages 11-12). In particular, it is clear from the passage noted by Applicant that Borque et al. contemplate that multiple different forms of lipoprotein(a) will bind to the particles, and therefore that multiple isoforms or "phenotypes" would be measured by the method.

Moreover, the methods of Borque et al. employ *polyclonal* antibodies, which were well known in the art to contain many different antibody molecules that bind to an antigen in many different ways (see Janeway et al., Immunobiology: the Immune System in Health and Disease

(1999), Elsevier Science Ltd/Garland Publishing, New York, NY, Fourth Edition, pages 34-35, especially at page 35, the second full paragraph; and Figure 2.1). For these reasons, the scientific evidence of record strongly suggests that the methods of Borque et al. would also measure multiple phenotypes of lipoprotein(a), and Applicant has not advanced any evidence to the contrary.

Applicant argues that the references of record to not suggest the use of arginine in amount of "12% or greater". See Reply, page 4, third paragraph.

This is not found persuasive because as currently amended, the claims no longer recite this limitation. In addition, the independent claim is not limited to any particular concentration of arginine.

Applicant's arguments that de Steenwinkel employs a chaotropic agent to *reduce* interferences while the claimed method employs arginine to *increase* protein-protein interactions were previously advanced in the Reply filed 7/27/2009 (see page 5) and are not persuasive for reasons of record (Office action mailed 10/5/2009 at pages 12-13).

Applicant argues that de Steenwinkel does not list arginine as an exemplary chaotropic agent. See Reply, pages 4-5.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, the Metzner et al. reference teaches that arginine is a known chaotropic agent, as acknowledged by Applicant (Reply, page 5). It is maintained for reasons of record that the selection of a known material for its known purpose would have been obvious.

Applicant further argues that one would not be motivated to use arginine because nothing in the reference of record suggests that arginine can be used "to circumvent the influence of variations in measurement values attributable to phenotypic differences" (reply, page 5, third paragraph).

This is not found persuasive because such a feature is neither recited nor clearly required by the claims. Furthermore, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In the instant case, de Steenwinkel et al. teaches the benefits of using chaotropic agents to reduce or overcome interferences in particle agglutination immunoassays (which describes the immunoassays of Borque et al.). For reasons of record, it is maintained that one would be motivated to select arginine as a known chaotropic agent in order to achieve this recognized benefit.

Arguments for the presence of unexpected results

Counsel further asserts unexpected results, namely the ability to detect phenotypic variants of lipoprotein(a) (Reply, page 5, third paragraph). As discussed in the rejection above, the preamble language "measuring lipoprotein(a) having several phenotypes" does not clearly require detection of phenotypic variants.

In addition, Applicant has not provided any evidence to rebut that already of record, which strongly suggests that the methods of Borque et al. would indeed detect multiple isoforms or phenotypes of lipoprotein(a).

Finally, as previously noted, the burden of proof rests on the party asserting unexpected results (previous Office action, pages 13-14). The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). To be of probative value, any objective evidence should be supported by actual proof. See MPEP 716.01(c). Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results.

In the instant case, Applicant has not advanced evidence to substantiate the existence of unexpected results.

Counsel further asserts unexpected results regarding correlation coefficients. Applicant argues that the data of Borque et al. exhibit a correlation coefficient of 0.956, while the data in the instant specification had a correlation coefficient of 0.973 (Reply, page 5, last paragraph). Applicant characterizes the correlation coefficient of Borque et al. as “low” and argues that Borque et al. acknowledges this low correlation. Applicant further argues that this difference in correlation coefficient (0.956 vs. 0.973) is "considerable" and speculates that it is “possible” that this difference arises due to variations in measurement values attributable to phenotypic differences.

The examiner does not agree with Applicant's interpretation of Borque. Applicant points to Borque et al. at page 871, right column, first paragraph in support of the contention that "[Borque] acknowledges this low correlation". However, in the first full sentence of this paragraph, Borque et al. state that:

> Correlation coefficients (r) ranged from 0.95…to 0.98…indicating a close correlation between all assays.

Consequently, the examiner finds insufficient evidence to adopt Applicant's interpretation of the reference as meaning that Borque et al. acknowledged their reported correlation coefficients as "low".

In addition, Applicant argues that Borque et al. report a correlation coefficient of 0.956 in Figures 3c and 3d, and contrasts this with a disclosed correlation coefficient of 0.973. However, the legend to Figure 3 of Borque et al. is as follows:

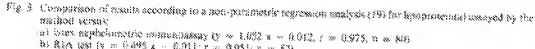
Fig. 3 Comparison of results according to a non-parametric regression analysis (39) for lipoprotein(a) assayed by the turbidimetric method versus:
a) Behring nephelometric immunoassay (y = 1.652 x − 0.012, r = 0.975, n = 86)
b) RIA test (y = 0.695 x − 0.013, r = 0.951, n = 52)
c) ELISA TintElize method (y = 1.760 x − 0.012, r = 0.978, n = 80)
d) ELISA, Macra method (y = 1.493 x − 0.025, r = 0.978, n = 80)

The examiner therefore was unable to find a correlation coefficient of "0.956" reported by Borque et al. for Figures 3c and 3d. According to the reference, the correlation coefficient for comparison with the two ELISA methods in Figures 3c and 3d is 0.978 in both cases (see above). Therefore, the correlation coefficient reported by Borque et al. (0.978) is actually higher than 0.973.

Even assuming for the sake of argument that the correlation coefficient(s) obtained by the methods of Borque et al. are different than those reported instantly, "it is not enough to show that

results are obtained which differ from those obtained in the prior art: that difference must be shown to be an unexpected difference." In re Klosak, 455 F.2d 1077, 1080 (CCPA 1972).

It has been long held that "even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art, unless the claimed ranges 'produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996) (quoting *In re Aller*, 220 F.2d 454, 456 (1955), and citing *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990)).

In the instant case, Applicant has not provided evidence to show what correlation coefficients would be *normally expected*, and how such statistical measures might normally differ from run-to-run or when different combinations of reagents were used in the two types of assays being compared.

Therefore, even assuming for the sake of argument that Borque et al. report a correlation coefficient of 0.956, Applicant has not provided a substantive explanation of why observing a correlation coefficient of 0.973 vs. 0.956 would be surprising or unexpected, beyond the assertion that this difference is "considerable". Such conclusory statements by counsel do not constitute sufficient evidence of unexpected results.

Furthermore, the disclosed correlation coefficient was obtained from a single assay run using a defined set of reagents, while the instant claims are not limited to any particular reagents and do not require any particular correlation coefficient to be achieved. As such, there is insufficient evidence that this represents an unexpected result that is commensurate with the scope of the claims.

Finally, the speculation by counsel as to the source of the observed difference in correlation coefficient fails to establish a nexus between the merits of the invention and the asserted secondary considerations of unexpected results. Applicant has not provided evidence to show that the differences between the claimed invention and that of Borque et al. are what give rise to the argued difference in correlation coefficient.

It is stated only that it is "possible" that the lower correlation coefficient reported by Borque et al. is due to "variations in measurement values attributable to phenotypic differences"; but neither a lower correlation coefficient nor its source has been adequately substantiated.

It is not clearly explained what technical or procedural differences are responsible for these possible variations, and how such features are reflected in the limitations recited in the claims. Applicant refers to different correlation coefficients obtained at different arginine concentrations (Reply, page 5, penultimate paragraph) but does not clearly argue or provide evidence to show that it is the presence of arginine which is responsible for the argued difference in results between the claimed invention and that of Borque et al.

If Applicant believes that the presence of arginine gives rise to an unexpected difference in terms of a particular level of correlation with ELISA methods, comparative evidence should be provided to document the criticality of arginine in this regard. Such evidence should be representative of the entire range claimed in order to be commensurate in scope with the claimed subject matter, which is not currently limited to any particular concentration of arginine.

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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